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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/465,322	06/05/95	SODERLUND	H	A28203-A-FWC

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EXAMINER	
MYERS,C	
ART UNIT	**PAPER NUMBER**
1655	30

DATE MAILED: 03/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/465,322	Soderlund
Examiner	**Group Art Unit**
Carla Myers	1655

☒ Responsive to communication(s) filed on *Dec 20, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *51-53, 56, 57, 59, 62, 63, 67, and 70-96* is/are pending in the applicat

Of the above, claim(s) *76-96* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *51-53, 56, 57, 59, 62, 63, 67, and 70-75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *27*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to Paper No. 29, filed December 20, 2000. Applicants arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made FINAL.

2. Newly submitted claims 76-96 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 51-53, 56, 57, 59, 62, 63, 67, and 70-75, drawn to kits comprising a polymerizing agent, a deoxynucleotide, a chain terminating agent and a primer, classified in class 435, subclass 6.

II. Claims 76-96, drawn to methods for determining the identity of a specific nucleotide, classified in class 435, subclass 6.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the kits of invention I can be used in a materially different process, such as for sequencing DNA.

Because these inventions are distinct for the reasons given above and have acquired a different status in the art as recognized by their divergent subject matter and because inventions I and II require different searches that are not co-extensive, examination of these distinct inventions

would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 76-96 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 56, 57, 59, and 62 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 56, 57, 59 and 62 are indefinite over the recitation of "kit according to claim 51 having the detection primer sequence" because it is unclear as to what is meant by a kit having a detection primer sequence and this phrase lacks proper antecedent basis since the claims previously refer to a detection primer, but not to a detection primer sequence. The claims should be amended to recite, for example, "A reagent kit according to claim 51, wherein the detection primer consists of the sequence of 5'-GTA CTG CAC CAG GCT GCC GC-3' ."

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 51-53, 63, 67, 70-75 are rejected under 35 U.S.C. § 103 as being unpatentable over Erlich (U.S. Patent No. 5,310,893) in view of Mullis (U.S. Patent No. 4,683,202; cited in the IDS of Paper No. 5).

Erlich (see, for example, col. 8) teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. In particular, Erlich teaches primer "DB01" (see columns 29 and 30), which hybridizes to the target nucleic acid so that the 3' nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second nucleotide residue. It is pointed out that the 3' residue of the DB01 primer flanks the "CTT" codon, which is present as a "GTG" codon in allelic variants and thereby the "C" nucleotide adjacent to the primer is considered to be a variable or mutated nucleotide and the "C" and "G" nucleotides are considered to be a first and a second "nucleic acid residue at a defined site". Erlich

teaches that primers may be 15 to 25 nucleotides in length (col. 4) and teaches that the DB01 primer is 21 nucleotides in length (col. 29). Erlich also teaches that, following the amplification reaction, the sequence of sample nucleic acids can be determined and confirmed by dideoxy chain termination sequencing. It is conventional in the field of dideoxy chain termination sequencing to use labeled dideoxyribonucleotide triphosphates to facilitate detection of the sequencing products. Erlich further teaches that the amplification reaction is performed using dNTPS and a polymerase. It is stated that the amplification may be performed using labeled reagents in order to allow for the detection of the amplification products and Erlich exemplifies methods in which the primers are labeled with detectable moieties (see, for example, col. 5). Erlich does not exemplify methods using labeled dNTPS. However, Mullis (col. 14) teaches that in PCR either the primer or the dNTPS may contain detectable moieties. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Erlich so as to have amplified the target nucleic acids using labeled dNTPs in place of labeled primers in order to have provided an equally effective means for facilitating detection of the amplification products. Such a modification of the method of Erlich would have resulted in a method which comprised the use of the reagents of a target nucleic acid, a DB01 oligonucleotide primer consisting of a sequence that hybridizes to the target nucleic acid immediately adjacent to a variable nucleotide position, labeled nucleotides and/or labeled dideoxynucleotide triphosphates, and a polymerase. Erlich does not specifically disclose a kit comprising each of these reagents. However, Erlich (col 26) does suggest that kits should be prepared containing all of the reagents required to practice the disclosed amplification technique wherein such kits comprise, for

example, a primer, the substrate nucleoside triphosphates, means used to label, and an agent used to catalyze primer extension. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated a kit for practicing the method of Erlich which contained the reagents of target nucleic acid, the DB01 amplification primer, labeled nucleotides or labeled dideoxynucleotides and a polymerase in order to have achieved the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claims 63 and 67, Erlich does not specifically exemplify a DB01 primer having attached thereto an "attachment moiety" through which the primer can be immobilized or immobilization of the primer and the amplification product onto a solid support. However, Erlich does teach that primers useful for amplifying variable nucleotides can be modified so as to attach labels thereto, including labels which can be used to capture the primer and facilitate immobilization of the primer onto a solid support (see col. 5). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the amplification primer of Erlich so as to have attached an affinity moiety to the primer to allow for the immobilization of the primer in order to have accomplished the expected advantage of generating a primer which could easily be immobilized onto a solid support to have allowed for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from other nucleic acids.

In the response of Paper No. 29, Applicants traversed the previous grounds of rejection by stating that the cited references do not teach use of both deoxynucleotides and chain terminating nucleotides. These arguments are not convincing because they are based on a separate analysis of the individual references and the separate methodologies taught by each reference. The response

does not address the rejection which is based on the combination of the Erlich and Mullis references and the complete teachings of each of these references. As discussed in the above rejection, the references when taken together suggest performing sequentially the methods of amplification and sequencing. The amplification method utilizes labeled dNTPs, polymerase and a primer which hybridizes immediately adjacent to the 3' end of a variable nucleotide. The sequencing method utilizes labeled chain terminating reagents, dNTPs and polymerase. Accordingly, the prior art when considered as a whole would have suggested the claimed kits comprising reagents for performing the disclosed amplification and sequencing reactions, particularly the reagents of deoxynucleotides, chain terminating nucleotides, a polymerase and a primer which hybridizes immediately adjacent to the 3' end of a variable nucleotide.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS. In particular, it is noted that the claims have been amended so that each claimed kit requires the presence of a chain terminating nucleotide and to delete the requirement that the kits contain "a labeled nucleotide complementary to a specific nucleotide at a predetermined position in the target nucleic acid polymer".

5. Claims 51, 53, 70, 72-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mundy (U.S. Patent No. 4,656,127; cited in IDS of Paper NO. 5).

Mundy et al disclose methods for detecting a target nucleic acid wherein the methods comprise hybridizing a primer to a target nucleic acid so that the primer terminates immediately upstream of a variable nucleotide; extending the primer using a polymerizing agent and a chain terminating reagent, wherein the primer is extended if the chain terminating agent is the

complement of the variable nucleotide; admixing the resulting product with one or more labeled nucleotides, so that the primer is extended to incorporate the nucleotides, if the chain terminating agent is not already linked to the primer (see column 3). Mundy teaches that the chain terminating reagent may be a dideoxynucleotide, and that different dideoxynucleotides are employed depending on the variable nucleotide to be detected. The reference also teaches that the nucleotide derivatives may be labeled (see column 6) and are at least 10 nucleotides in length (column 5). Primers may also be employed which do not terminate immediately adjacent to the variable nucleotide, in which case one or more nucleotides (dATP, dCTP, dGTP and/or dTTP) are included in the chain terminating reaction (see for example claim 7). The target nucleic acid may be bound to a solid support such that the resulting primer extension product is immobilized onto a solid support (see column 4). Accordingly, the method of Mundy requires the use of a primer which hybridizes upstream of a variable nucleotide to be detected, a polymerizing reagent, labeled nucleotides, and chain terminating reagents. Mundy does not teach packaging the reagents required to package the detection method in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primer, polymerizing agent, dideoxynucleotides and labeled nucleotides in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect mutations in target nucleic acids.

6. Claims 56-57 are rejected under 35 U.S.C. § 103 as being unpatentable over Mundy in view of Emi (Genomics (1988) 3:373-379).

The teachings of Mundy are presented above. In particular, Mundy teaches that the primer comprises sequences complementary to the target nucleic acid and that the primer terminates immediately 3' to the predetermined nucleotide position. It is stated that the detection method can be used to detect nucleotide variation in any target gene, including the beta-globin gene and ras oncogene (col. 1-2). However, Mundy does not specifically teach primers for detecting mutations in the ApoE gene. Emi teaches allele specific probes for detecting mutations in the apoE gene. Furthermore, at the time the invention was made the complete sequence of the apoE gene was known. In view of the teachings of Mundy of how to select primers for detecting nucleotide variation and in view of the teachings of Emi of the specific mutations in the apoE gene and the disclosure of allele specific probes for detecting these mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers comprising sequences complementary to the apoE gene immediately flanking the modified nucleotide encoding codons 112 and 158 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of sequence variation in the apoE gene.

7. Claim 59 is rejected under 35 U.S.C. § 103 as being unpatentable over Mundy in view of Saiki (Nature (1986) 324:163-166).

The teachings of Mundy are presented above. In particular, Mundy teaches that the primer comprises sequences complementary to the target nucleic acid and that the primer terminates immediately 3' to the predetermined nucleotide position. . It is stated that the detection method can be used to detect nucleotide variation in any target gene (see columns 1-2).

However, Mundy does not exemplify primers for detecting mutations in the beta-globin gene. Saiki teaches allele specific probes for detecting mutations (A to T) in codon 6 of the beta-globin gene. Furthermore, at the time the invention was made the complete sequence of the beta-globin gene was known. In view of the teachings of Mundy of how to select primers for detecting nucleotide variation and in view of the teachings of Saiki of the specific mutation in the beta globin gene leading to sickle cell anemia and the disclosure of allele specific probes for detecting this mutation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers comprising sequences complementary to the beta-globin gene immediately flanking the modified nucleotide encoding codon 6 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of the sickle cell mutation.

8. Claim 62 is rejected under 35 U.S.C. § 103 as being unpatentable over Mundy in view of Farr et al (PNAS (1988) 85:1629-1633; cited on IDS of Paper No. 5).

The teachings of Mundy are presented above. In particular, Mundy teaches that the primer comprises sequences complementary to the target nucleic acid and that the primer terminates immediately 3' to the predetermined nucleotide position. It is stated that the detection method can be used to detect nucleotide variation in any target gene (columns 1-2). However, Mundy does not exemplify primers for detecting mutations in the ras oncogene. Farr teaches allele specific probes for detecting mutations in codon 12 of the ras oncogene (see Table 1). Furthermore, at the time the invention was made the complete sequence of the ras oncogene was

known. In view of the teachings of Mundy of how to select primers for detecting nucleotide variation and in view of the teachings of Farr of the specific mutations in the ras oncogene and the disclosure of allele specific probes for detecting these mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers of about 18 nucleotides comprising sequences complementary to the ras oncogene immediately flanking the modified nucleotide encoding codon 12 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of genetic variation in the ras oncogene.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

March 1, 2001

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER